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P h a r m a c e u t i c a l s

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**MERCK/SCHERING-PLOUGH PHARMACEUTICALS COMMENTS  
ON RESULTS OF THE ENHANCE STUDY**

**STUDY PRESENTED AT AMERICAN COLLEGE OF CARDIOLOGY  
SCIENTIFIC SESSIONS AND PUBLISHED IN ON-LINE VERSION OF  
*THE NEW ENGLAND JOURNAL OF MEDICINE***

Chicago, March 30, 2008 – Results of ENHANCE (Ezetimibe and simvastatin in Hypercholesterolemia enhances atherosclerosis regression), an imaging trial in 720 patients with heterozygous familial hypercholesterolemia (HeFH), a rare genetic condition that causes very high levels of LDL “bad” cholesterol and greatly increases the risk for premature coronary artery disease, were presented at the 57<sup>th</sup> Annual Scientific Sessions of the American College of Cardiology and also were published on-line in *The New England Journal of Medicine*<sup>1</sup>.

As previously reported on January 14, 2008, despite the fact that ezetimibe 10 mg plus simvastatin 80 mg significantly lowered LDL “bad” cholesterol more than simvastatin 80 mg alone, there was no significant difference between treatment with ezetimibe plus simvastatin and simvastatin alone on the pre-specified primary endpoint: a change in the thickness of carotid artery walls over two years as measured by ultrasound. There also were no significant differences between treatment with ezetimibe plus simvastatin and simvastatin on the four pre-specified key secondary endpoints: per cent of patients manifesting regression in the average carotid artery intima-media thickness (CA IMT); proportion of patients developing new carotid artery plaques >1.3 mm; changes in the average maximum CA IMT; and changes in the average CA IMT plus changes in the average common femoral artery IMT.

In ENHANCE, when compared to simvastatin alone, ezetimibe plus simvastatin significantly lowered LDL “bad” cholesterol, as well as triglycerides and C-reactive protein (CRP). In the ENHANCE study, as previously reported, the overall safety profile of ezetimibe plus simvastatin in the study was generally consistent with their product labels.

“While ENHANCE showed no statistical difference between treatment arms in mean IMT, it did show once again that combining ezetimibe with simvastatin lowers LDL-C significantly more than simvastatin alone,” said Dr. Daniel Gaudet, ENHANCE study investigator, Professor of Medicine at University of Montreal and Director of research at the Chicoutimi University Hospital Lipid Clinic. “Over 30 years of science have confirmed that elevated LDL-C is a major risk factor for cardiovascular disease, and we must continue to treat patients for high cholesterol in light of the strong body of evidence we currently have.”

In the ENHANCE publication, the authors provided three theoretical explanations why, despite ezetimibe plus simvastatin significantly lowering LDL “bad” cholesterol more than simvastatin (56 per cent vs. 39 per cent,  $p < 0.01$ ), there was no significant difference between treatment groups on the primary endpoint and four key secondary endpoints: (1) lowering of LDL cholesterol with non-statin therapy, such as ezetimibe, might affect IMT differently than statin therapy, (2) the imaging technology selected was not sensitive enough to detect a difference, or (3) that these HeFH patients were extensively pretreated with lipid-lowering therapy, thereby limiting the amount that CA IMT could change with further LDL cholesterol-lowering therapy, consequently limiting the ability to detect a differential response to the two treatments. The authors concluded that the reason for the failure to observe an incremental effect on CA IMT thickness in spite of a reduction in the level of LDL cholesterol remains unknown.

In the publication, the authors addressed the premise that the lack of a difference in the change of mean CA IMT between ezetimibe plus simvastatin and simvastatin alone, despite greater LDL cholesterol-lowering, could be attributed to lipid-independent effects of statins on arteries. The authors presented several facts that argued against this concept, including a discussion of clinical studies involving statin and non-statin therapeutic approaches that demonstrated cardiovascular risk reductions were associated with the degree of LDL-cholesterol lowering. The authors suggested that clinical outcomes data are needed to answer this question.

As for the hypothesis that the results may reflect the imaging technology, the authors noted this seems unlikely given the precision of the imaging measurement results seen in the ENHANCE trial.

With respect to the hypothesis that the ENHANCE results were due to the characteristics of the patients studied, the authors pointed out that in an earlier imaging study (extension of ASAP or **A**torvastatin vs. **S**imvastatin on **A**therosclerosis **P**rogression study) use of potent lipid-lowering therapy in HeFH patients produced "regression" or "thinning" of CA IMT during the first one to two years of therapy, but further decreases during the following two years on the same therapy were not seen. In ENHANCE, approximately 80 per cent of the enrolled patients reported taking statin treatment at the time of screening for the study, and had a mean baseline CA IMT of 0.69 to 0.70 mm. In another recent IMT study in HeFH patients (**R**ADIANCE 1 or **R**ating **A**therosclerotic **D**isease **C**hange by **I**maging with **A** **N**ew **C**ETP Inhibitor study), the baseline CA IMT was also lower than in the earlier IMT study and similar to ENHANCE and, importantly, the pattern of change in CA IMT in this IMT study was very similar to that observed in both treatment groups in the ENHANCE study.

The authors noted that “these data raise the possibility that there may be limits to the extent to which the lowering of LDL cholesterol levels can result in a further decrease in the progression of intima-media thickness in the context of previous statin therapy and a modest baseline intima-media thickness <sup>2</sup>.”

"Although a definitive explanation is never possible with a finding like this, we believe that the most likely explanation for the failure to see a significant difference between treatment groups in ENHANCE relates to the behavior of IMT in this population of HeFH patients," noted Thomas Musliner, M.D., Executive Director, Cardiovascular Disease, Clinical Research, Merck Research Laboratories. "The large majority of these patients were previously treated with LDL cholesterol-lowering therapy and presumably experienced an effect in CA IMT from that treatment, as reflected in the patients' relatively low CA IMT values when they began the study. The findings of the ASAP extension, RADIANCE 1 and ENHANCE suggest there are limits to how much IMT can be decreased in HeFH study cohorts in the context of the widespread and prolonged use of effective LDL cholesterol-lowering treatment starting at an earlier age, which is now the standard of care for these patients."

### **Endpoint Data and Cardiovascular Events**

ENHANCE investigators found no statistically significant difference between the two treatment groups on the primary endpoint: the change in the average CA IMT at three carotid artery locations. The change from baseline in the mean (average) CA IMT in the ezetimibe plus simvastatin group was 0.0111 mm, which did not significantly differ from the simvastatin group's change of 0.0058 mm ( $P=0.29$ ). The median data for the primary endpoint, which also showed no statistical difference between treatments, was 0.0058 mm in the ezetimibe plus simvastatin group and 0.0095 mm for the simvastatin group. The treatment groups also did not have statistically significant differences for each of the three carotid artery locations that comprised the primary endpoint: the common carotid, the internal carotid and the carotid bulb.

The ENHANCE study was not designed nor powered to evaluate cardiovascular clinical events. IMPROVE-IT is underway and is designed to provide cardiovascular outcomes data for ezetimibe plus simvastatin in patients with acute coronary syndrome. No incremental benefit of ezetimibe plus simvastatin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

### **Lipid Parameters of LDL Cholesterol, Triglycerides and HDL Cholesterol; and C-reactive Protein**

Over the two-year period of the ENHANCE study based upon the "last observation carried forward" endpoint approach, the group treated with ezetimibe plus simvastatin had a 56 per cent mean reduction of LDL cholesterol (from a baseline of 319 mg/dL or 8.25 mmol/L) that was significantly greater than the 39 per cent mean reduction of LDL cholesterol (from a baseline of 318 mg/dL or 8.22 mmol/L) in the group treated with simvastatin alone ( $P<0.01$ ).

In addition, by study completion, the ezetimibe plus simvastatin group had a 30 per cent median reduction in triglycerides (from baseline 157 mg/dL or 1.77 mmol/l), significantly more than the 23 per cent median reduction (from baseline 160 mg/dL or 1.81 mmol/L) in the simvastatin group ( $P<0.01$ ). Also, the ezetimibe plus simvastatin group had a 49 per cent median reduction in CRP (from baseline 1.70 mg/L), significantly more than the 24 per cent median reduction in CRP (from baseline 1.70 mg/L) in the simvastatin group ( $P<0.01$ ). The ezetimibe plus simvastatin group had a 10 per cent increase (from baseline 46.7 mg/dL or 1.21 mmol/L) in HDL "good" cholesterol; the simvastatin group had an 8 per cent increase from baseline 47.4 mg/dL or 1.23 mmol/L ( $P=0.05$ , no statistical significance).

### **Tolerability Data**

As previously reported, the overall safety profiles of ezetimibe and simvastatin were similar and generally consistent with their product labels. Both medicines were generally well tolerated. Also, the overall incidence rates of treatment-related adverse events were 34 per cent for ezetimibe plus simvastatin (122/357) and 29 per cent (107/363) for simvastatin only; the incidence rates for discontinuations due to adverse events were 8.1 per cent for ezetimibe plus simvastatin (29/357) and 9.4 per cent for simvastatin only (34/363).

### **About the Study Design and Methodology**

The ENHANCE study was an international two-year, randomized, double-blind, controlled trial in 720 HeFH patients between the ages of 30 to 75. All of the ENHANCE patients had HeFH, which affects approximately 0.2 per cent of the population. The rationale for studying HeFH patients is that these patients are known to be at increased risk for premature coronary artery disease and, if untreated, exhibit increased IMT progression rates beginning in childhood. Prior LDL cholesterol-lowering therapy of any kind was not an exclusion criterion for ENHANCE, although such therapies were discontinued at the start of the study. Also, there was not a minimum value for CA IMT specified for inclusion in study. Following a six-week, single blind, placebo lead-in/drug "wash-out" period, patients were randomized to receive either daily ezetimibe 10 mg and simvastatin 80 mg (N=357) or daily simvastatin 80 mg (N=363).

ENHANCE investigators took digitized single-frame CA IMT images at the three locations of the patients' right and left carotid arteries. These images were taken at several time points: study baseline, 6, 12, 18 and 24 months.

"Examination of the CA IMT collected during ENHANCE proved to be a far more challenging process than originally anticipated when the study design was drawn up. Therefore, preparation of the images for entry into a database took significantly longer than expected, as the blinded investigators and CA IMT evaluators took numerous steps in 2006 and 2007 to address image quality control and finalize the analysis," said Enrico P. Veltri, M.D., co-author of the ENHANCE study publication and group vice president, Cardiovascular and Metabolic Disease, Clinical Research, Schering-Plough Research Institute. "Our companies acted with integrity and good faith in connection with the trial," he said.

### **About Merck Frosst/Schering Pharmaceuticals**

Merck Frosst/Schering Pharmaceuticals (MFSP) is a joint venture between Merck Frosst Canada Ltd. and Schering-Plough Canada Inc., which was established in December 2001 as part of a worldwide partnership (except Japan) between the two companies. MFSP was formed to develop and market new prescription medicines for the management of cholesterol.

### **Merck Forward-Looking Statement**

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1A of Merck's Form 10-K for the year ended Dec. 31, 2007, and in its periodic reports on Form 10-Q and Form 8-K, which the Company incorporates by reference.

### **Schering-Plough Disclosure Notice**

The information in this press release includes certain "forward-looking statements" within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, including statements relating to potential market for EZETROL® (ezetimibe). Forward-looking statements relate to expectations or forecasts of future events. Schering-Plough does not assume the obligation to update any forward-looking statement. Many factors could cause actual results to differ materially from Schering-Plough's forward-looking statements, including market forces, economic factors, product availability, patent and other intellectual property protection, current and future branded, generic or over-the-counter competition, the regulatory process, and any developments following regulatory approval, among other uncertainties. For further details about these and other factors that may impact the forward-looking statements, see Schering-Plough's Securities and Exchange Commission filings, including Part I, Item 1A. "Risk Factors" in the Schering-Plough's 2007 10-K/A.

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<sup>1</sup> N Engl J Med 2008; 358: 1431-43.

<sup>2</sup> N Engl J Med 2008; 358: 1431-43.